**Amendment to the claims**

The listing of claims will replace all prior versions, and listings of claims in the application.

**Listing of claims**

Claims 1-7 (cancelled)

8. (cancelled) A method of detecting a human disease state, comprising the steps of:

a) detecting the quantity of a disease marker expressed in human peripheral blood; and

b) comparing the quantity of said marker to the quantity expressed in peripheral blood of a normal individual;

wherein a difference in quantity of expression is indicative of a disease state.

9. (currently amended) A method of detecting a human disease state, comprising the steps of: ~~The method of claim 8, wherein said~~

a) detecting the quantity of a disease marker ~~is an~~ mRNA expressed in human peripheral blood; and

b) comparing the quantity of said marker to the quantity expressed in peripheral blood of a normal individual;

wherein a difference in quantity of expression is indicative of a disease state.

10. (original) The method of claim 9, wherein said mRNA is amplified by an RNA polymerase reaction.

11. (original) The method of claim 9, wherein said mRNA is amplified by reverse transcriptase polymerase chain reaction or the ligase chain reaction.

12. (currently amended) The method of claim [[8]] 9, wherein said detecting is by RNA fingerprinting, branched DNA or a nuclease protection assay.

13. (currently amended) The method of claim [[8]] 9, wherein the disease state is metastatic cancer, asthma, lupus erythromatosis, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, autoimmune thyroiditis, ALS (Lou Gehrig's disease), interstitial cystitis or prostatitis.

14. (currently amended) The method of claim [[8]] 9, wherein the disease state is metastatic cancer.

15. (original) The method of claim 14, wherein the metastatic cancer is metastatic prostate cancer.

16. (original) The method of claim 14, wherein the metastatic cancer is metastatic breast cancer.

17. (original) The method of claim 9, in which said mRNA comprises one or more of the sequences or the complements of the sequences disclosed herein as SEQ ID NO: 1, SEQ ID N0:2, SEQ ID N0:3, SEQ ID NO:29, SEQ ID N0:34, SEQ ID NO:48 or SEQ ID NO:49.

18. (currently amended) The method of claim [[8]] 9 in which said marker is a product of an interleukin 8 (IL-8) or interleukin 10 (IL- 10) gene.

19. (original) The method of claim 9, further comprising the steps of

a) providing primers that selectively amplify said disease state marker;

b) amplifying said nucleic acid with said primers to form nucleic acid amplification products;

c) detecting said nucleic acid amplification products; and

d) measuring the amount of said nucleic acid amplification products formed.

20. (original) The method of claim 19 in which said primers are selected to specifically amplify a nucleic acid having a sequence comprising SEQ ID NO:1, SEQ ID N0:2, SEQ ID NO:3, SEQ ID N0:29, SEQ ID NO:34, SEQ ID N0:48 or SEQ ID NO:49.

21. (withdrawn) The method of claim 8, wherein said marker is a polypeptide.

22. (withdrawn) The method of claim 21, wherein said polypeptide is encoded by a nucleic acid sequence comprising the sequence disclosed herein SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO: ID NO:3, SEQ ID N0:29, SEQ ID NO:34, SEQ ID NO:48 or SEQ ID N0:49.

23. (withdrawn) The method of claim 21, wherein said detection is by an antibody immunoreactive with said marker.

24. (withdrawn) The method of claim 21, wherein said polypeptide is encoded by an IL-8 or IL-I0 gene.

25. (withdrawn) The method of claim 8, wherein said marker is a product of the IL-8 gene and wherein said comparison is between two alternatively spliced forms of an IL-8 gene product.

26. (withdrawn) The method of claim 24, wherein the quantity of IL-8 polypeptide in peripheral blood is measured using an in vitro bioassay that detects an IL-8 mediated biological process.

27-63 (cancelled)

64. (original) The method of claim 19, in which said primers are selected to specifically amplify a nucleic acid product of the IL- 10 gene.

65. (withdrawn) The method of claim 24, wherein the quantity of IL-10 polypeptide in peripheral blood is measured using an in vitro bioassay that detects at least one IL-10 mediated biological process.

Claims 66-73 (cancelled)

## A. Status of the Claims

Claims 8-20 and 64 were pending with claims 21-26 and 65 being withdrawn from further consideration as being drawn to a non-elected invention. Claim 8 is cancelled herein and claim 9 has been written in independent form. Claims 12-14 and 18 have been amended to depend from claim 9 instead of claim 8.

## B. Rejections Under 35 U.S.C. §112, First Paragraph – Written Description

The Action rejects claims 8-20 and 64 under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. The Action states that the specification does not clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed. Applicants respectfully traverse.

To satisfy the written description requirement a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the ***claimed invention*** (MPEP 2163 citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991)). In regard to originally filed claims, the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention as defined by the originally filed claims. (*In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1076)).

Applicants note that claims 8-20 and 64 are originally filed claims. Furthermore, the amended claims are directed to a ***method of detecting*** the quantity of a disease marker mRNA in the peripheral blood and comparing the quantity of the disease marker in a sample with the quantity of the disease marker in normal individuals' blood. The amended claims do not claim a disease marker, but claim a method of detecting disease states by analysis of peripheral blood.

The Action admits on page 6 that Applicants have provided methods of identifying disease markers. The Action states that the various disease markers disclosed in the application are insufficient, but does not provide any reasoning or support as to why this is so.

The specification provides sufficient description of the method to convey to one of skill in the art that the inventors had possession of the claimed method for detecting a human disease state(s). For example amended claim 9, which is originally filed claim 9 written in dependent form, reads as follows:

> A method of detecting a human disease state, comprising the steps of: a) detecting the quantity of a disease marker mRNA expressed in human peripheral blood; and b) comparing the quantity of said marker to the quantity expressed in peripheral blood of a normal individual; wherein a difference in quantity of expression is indicative of a disease state.

In addition to the description provided by the originally filed claims, the specification provides written description of the claimed method, at least on pages 8, lines 10-27; page 85-92; and in the examples on pages 100-161. The specification states on page 8, lines 20-27:

> The instant invention addresses the problem of diagnosing human disease states by detecting a secondary response to a given disease state that may be measured in peripheral blood samples. A preferred embodiment involves monitoring gene expression in peripheral leukocytes of the immune system. A number of disease states are capable of producing an immune system response, such as asthma, lupus erythromatosis, rheumatoid arthritis, multiple sclerosis , myasthemia gravis, autoimmune thyroiditis, ALS (Lou Gehrig's disease), interstitial cystitis and prostatitis. The methods disclosed herein may be suitable for detection of these diseases, as well as cancers from a variety of tissue sources.

The Action's arguments based on description of cDNA structure are irrelevant. Furthermore, exemplary methods for detection and quantification of RNA species is provided on pages 85 to 100. Specific examples are also provided on pages 100-161 of the specification that describe the use of the claimed method for the detection of disease markers for a metastatic cancer, *i.e.*, metastatic breast or prostate cancer.

The unrebutted presumption is that one of skill in the art would have understood that the inventors were in possession of the claimed method of detecting a human disease state(s) as originally claimed. The steps of the ***diagnostic method*** are clear. While the claims may encompass the use of compositions not specifically exemplified or identified the claims do require that there is a difference in the expression of the disease marker mRNA relative to diseased and normal peripheral blood. The claims encompass a method of diagnosis and not a disease marker composition or a method of identifying a disease marker. Applicants emphasize that the present claims are method of detection claims, and thus, as evinced by the foregoing, one of skill in the art would reasonably conclude that the inventor had possession of a method of detecting a human disease state. The method comprising detecting the quantity of a disease marker mRNA expressed in human peripheral blood; and b) comparing the quantity of said marker to the quantity expressed in peripheral blood of a normal individual; wherein a difference in quantity of expression is indicative of a disease state. Applicants respectfully request the withdrawal of the rejection.

**C. Rejections Under 35 U.S.C. §112, First Paragraph**

Claims 8-20 and 64 stand rejected under the first paragraph of 35 U.S.C. §112 as allegedly failing to enable any person skilled in the art to which the invention pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope to the claimed invention without undue experimentation. In particular, failing to enable a method of detecting a human disease state by detecting the quantity of a disease marker mRNA expressed in human peripheral blood; and b) comparing the quantity of said marker to the quantity expressed in peripheral blood of a normal individual; wherein a difference in quantity of expression is indicative of a disease state . Applicants respectfully traverse.

To satisfy the enablement requirement of 35 U.S.C. 112, first paragraph, the claimed invention must be described in such a way as to contain sufficient information regarding the claimed invention as to enable one skilled in the art to make and use the claimed invention without undue experimentation. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied. Applicants note, in regard to basing an enablement rejection on a reference to a written description rejection, that the enablement and written description requirements are distinct (*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991)).

In order for the Action to put forth an enablement rejection a reasonable basis to question the enablement must be provided. (*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1509, 1513 (Fed. Cir. 1993)). The Action fails to set forth any reason why one of skill in the art would not be able to detect a human disease state by a) detecting the quantity of a disease marker mRNA expressed in human peripheral blood; and b) comparing the quantity of said marker to the quantity expressed in peripheral blood of a normal individual; wherein a difference in quantity of expression is indicative of a disease state, as described in the present claims and specification. Applicants note again, that claims are directed to a method of detection not a disease marker mRNA.

Applicants provide several working examples of the claimed methods. For example, the specification on pages 108 to 112 and 136 to 146 describes exemplary methods that detect human metastatic breast and metastatic prostate cancer by detecting the quantity of a IL-8 mRNA expressed in human peripheral blood from either metastatic breast cancer or metastatic prostate cancer patients; and comparing the quantity of the IL-8 marker to the quantity of IL-8

expressed in peripheral blood of normal individuals; wherein a difference in quantity of expression is indicative of a disease state. The Action provides no reason why IL-8 or other disease markers would not be a viable marker for other cancers or other disease states. Particularly, since IL-8, for example, is expressed in peripheral blood cells in response to the disease condition and is not itself specific for a diseased cell. One of skill in the art would readily be able to extend, without undue experimentation, the claimed methods to other disease markers that are indicative of a disease state when there is a difference in the quantity of disease marker mRNA expressed in the peripheral blood.

**D. Rejection of Claims Under 35 U.S.C. §102 (b)**

The action has rejected claims 8, 13, 14 and 16 under 35 U.S.C. §102 as allegedly being anticipated by Heidenreich *et al.* (1979). Applicants have rewritten claim 9 as an independent claim and have amended claims 12-14 and 18 to depend from claim 9 instead of claim 8. Applicants reserve the right to pursue the subject matter of claim 8 in a future continuation application(s).

In view of the foregoing, removal of the rejection is respectfully requested.

## E. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. The examiner is invited to contact the undersigned (713) 651-5391 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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